IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	:	09/779,560	Confirmation No.:	6162
Appellant	:	Marianne Harboe		
Filed	:	February 9, 2001		
Title	:	METHOD FOR PROVIDING POLYPEPTIDE PREPARATIONS WITH REDUCED ENZYMATIC SIDE ACTIVITIES		
TC/Art Unit	:	1656		
Examiner:	:	DAVID J. STEADMAN		
Docket No.	:	58982.000002		
Customer No.	:	**21967**		

APPEAL BRIEF

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In response to the Final Office Action dated December 11, 2006 (hereinafter, the "Final Office Action"), finally rejecting pending claims 5, 6, 9-14, 16-18, 29-31, 35, 36, 39, 42, and 43, Appellant respectfully requests that the Board of Patent Appeals and Interferences (hereinafter, the "Board") reconsider and withdraw the rejections of record, and allow the pending claims, which are attached hereto as the Claims Appendix.

I. REAL PARTY IN INTEREST

The real party in interest is Chr. Hansen A/S, the sole assignee of the above-referenced application.

II. RELATED APPEALS AND INTERFERENCES

Appellant is unaware of any related appeals or interferences.

III. STATUS OF CLAIMS

Claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 are pending. Claims 1-4, 7-8, 15, 19-34, 37-38, and 40-41 are cancelled. The rejection of claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 is appealed.

IV. STATUS OF AMENDMENTS

The claim amendment submitted on October 31, 2006 was entered by the examiner. Appellant submitted no claim amendments subsequent to the Final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention involves a method of reducing glucoamylase activity in a chymosin-containing composition. Specifically, the claimed invention is directed to a method

that involves subjecting the composition to a pH in the range of 1.0 to 1.8 for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity. The unexpected results are shown experimentally by reference to Table 2.1, which shows the residual milk clotting activity (chymosin activity) of an embodiment of the invention, and Fig. 1, which shows the reduction in glucoamylase activity as a result of the present invention. This experimental evidence in the specification shows that by lowering the pH to a specified range, glucoamylase side activity is unexpectedly reduced while chymosin activity is maintained in significant quantities. These unexpected results are reflected in the claims by reference to the (1) the pH range over which they occur and (2) the actual result obtained in terms of residual glucoamylase and chymosin activity.

The specification teaches that the invention works on chymosin compositions, whether "they [are] derived from extracts of plant, animal or microbial cells naturally producing these products or . . . appropriate recombinant microbal host organisms producing the desired product(s) either being accumulated intracellularly or excreted into the cultivation medium." Specification , page 1, lines 19-22. However, the pending claims involve chymosin compositions that are derived from the cultivation of an organism that is selected from the group consisting of a bacterial species, a yeast species and a species of filamentous fungi, wherein the organism comprises a gene for encoding chymosin that is derived from a bovine or *Camelidae* species. The specification recognizes a particular problem with regard to chymosin compositions prepared using recombinant host organisms. Specifically, "[i]n certain instances, an undesired enzymatic activity in a cultivation medium for a recombinant organism is derived from the fact that the desired product is produced as a fusion protein of the desired gene product and a fusion partner having, in relation to the final product, an undesired enzymatic side activity." Specification, page 1, lines 25-30. An example is provided beginning on page 9 of the

specification where glucoamylase activity is inactivated in a recombinant chymosin preparation expressing a prochymosin-glucoamylase fusion protein.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellant seeks review of the following rejections set forth in the Final Office Action mailed December 11, 2006. The rejection of claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for failure to meet the written description requirement. The rejection of claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The rejection of claims 5-6, 9, 12-14, 16-18, and 42-43 as being unpatentable over U.S. Patent No. 5,801,034 ("Lawlis") in view of Ward et al., "Improved Production of Chymosin in Aspergillus by Expression as a Glucoamylase-Chymosin Fusion," Biotechnology Vol. 8, May 1990, pp. 435-440 ("Ward").

VII. ARGUMENT

A. The Pending Claims Satisfy the Written Description Requirement of 35 U.S.C. § 112, First Paragraph.

The specification unambiguously discloses that the invention is applicable where chymosin activity is accompanied by unwanted glucoamylase activity. *See, e.g.*, Example 1, page 9. The specification teaches that the problem of unwanted glucoamylase activity can arise in the context of recombinant chymosin producing organisms. *See* Example 1, page 9, *see also* page 1, lines 25-30. Claim 9, the sole independent claim, states:

> A method for reducing the glucoamylase activity in a milk clotting composition comprising the steps of:
>
> (i) providing a medium having a pH of 2.0 or higher that comprises chymosin activity and glucoamylase activity, wherein the medium having a pH of 2.0 or higher is derived from the cultivation of an organism that is

> selected from the group consisting of a bacterial species, a yeast species and a species of filamentous fungi, wherein the organism comprises a gene for encoding chymosin that is derived from a bovine or *Camelidae* species, and
>
> (ii) subjecting said medium to a pH in the range of 1.0 to 1.8 for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity.

Thus, the claimed invention involves a method that can be applied to media produced using certain recombinant organisms. The rejection for lack of written description appears to focus on the description of the recombinant organisms themselves. Specifically, the examiner has alleged two reasons why the claimed invention lacks written description under 35 U.S.C. § 112, first paragraph. First, the examiner contends that "the specification discloses only a single representative species of the recited genus of chymosin genes, i.e., bovine chymosin and *fails to disclose the structure of any mutants of bovine chymosin* that maintain the required 75% chymosin activity following pH treatment at a pH range of 1.0 to 1.8." Final Office Action, page 4 (emphasis added). Second, the examiner contends that "the specification and prior art nonetheless fail to adequately describe the recited genus of genes encoding a *Camelidae* chymosin or any mutant forms thereof." (*Id.*)

"To satisfy the written description requirement, a patent specification must described the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." M.P.E.P. § 2163 I (citing *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.) "There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." M.P.E.P 2163 I.A (citing *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). "Compliance with the written description requirement is essentially a fact-based inquiry

that will 'necessarily vary depending on the nature of the invention claimed.'" M.P.E.P. § 2163 I (citing *Enzo Biochem*, 323 F.3d at 963, 63 USPQ2d at 1613.) Finally, "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." *Falkner v. Inglis*, 79 USPQ2d 1001, 1008 (citing *Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 USPQ2d 1078 (Fed. Cir. 2005).

The examiner does not dispute that each and every claim limitation is found in the specification and claims as originally filed. *See* Final Office Action, page 4, lines 15-22. The written description rejection set forth in the Final Office Action instead finds the level of the disclosure in the specification inadequate to support the claims under the written description requirement.

The specification discloses "the surprising discovery that undesired enzymatic activities in polypeptide preparations can be reduced or eliminated by a very simple process step of subjecting the preparation to low pH for an appropriate period of time without any significant concurrent inactivation of the active polypeptide contained in the preparation." Specification, page 3, lines 30-33.

The pending claims state bovine or *Camelidae* species. However, the claims as a whole are not directed merely to "an organism that is selected from the group consisting of a bacterial species, a yeast species and a species of filamentous fungi, wherein the organism comprises a gene for encoding chymosin that is derived from a bovine or *Camelidae* species," but include the process steps for solving a problem that the specification teaches arises from the use of such recombinant organisms. Specifically, "[i]n certain instances, an undesired enzymatic activity in a cultivation medium for a recombinant organism is derived from the fact that the desired

product is produced as a fusion protein of the desired gene product and a fusion partner having, in relation to the final product, an undesired enzymatic side activity." Specification, page 1, lines 25-30. Furthermore, the specification provides an example of reducing glucoamylase activity derived from the cultivation of an organism expressing a prochymosin-glucoamylase fusion protein at page 9. The question raised by the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification would demonstrate to a person having ordinary skill in the art was in possession of the invention. When one considers the actual invention set forth in the claims, there is no doubt that the inventors were in possession of that invention at the time of filing.

Under these circumstances it is improper for the examiner to require additional disclosure related to the specific organisms which might be used with the method of the pending claims. The claims are not directed to recombinant organisms themselves and, as such, do not require the same level of disclosure that would be required had the claims been directed to broad claims to the organisms themselves. However, the examiner has analyzed the claims as though they were simply directed to the organisms themselves. Indeed, not once are the specific method steps of the claimed invention mentioned anywhere in the examiner's written description analysis. Appellant respectfully submits that when the claimed invention is considered as a whole there is no doubt that the specification conveys to the person of ordinary skill in the art that the applicant was in possession of the invention. Appellant further submits that the additional disclosure which the examiner would find necessary to comply with the written description requirement is not required under 35 U.S.C. § 112, first paragraph. Accordingly, Appellant respectfully requests that the honorable Board reverse the rejection of claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for failure to comply with the written description requirement.

B. The Pending Claims Are Enabled Under 35 U.S.C. § 112, First Paragraph.

It is well established that a patent must teach one of skill in the art how to make and use the claimed invention. 35 U.S.C. §112 ¶ 1. In considering whether a claimed invention is enabled under 35 U.S.C. § 112, first paragraph, the inquiry focuses on whether any necessary experimentation to perform the invention would be "undue." The factors to be considered in the enablement inquiry include: (A) The breadth of the claims, (B) the nature of the invention, (C) the state of the prior art, (D) the level of ordinary skill, (E) the predictability of the art, (F) the amount of direction provided by the inventor, (G) the existence of working examples, and (H) the quantity of experimentation need to make and use the invention based on the content of the disclosure. M.P.E.P. § 2164.01(a). The examiner did not provide analysis of these factors in the Final Office Action, and instead referred to the previous office action. The *Appellant* would note that the claims were amended after the prior office action and before the Final Office Action was mailed.

The Final Office Action fails to properly consider the scope of the claims. The claims are drawn to a process for reducing glucoamylase activity in certain recombinant chymosin compositions. The examiner postulates a broad interpretation of the materials for which the process of the invention can be applied and then proceeds to find a lack of enabling disclosure for every particular variant of starting material that might be included in the claimed invention. However, the specification teaches that "[i]n certain instances, an undesired enzymatic activity in a cultivation medium for a recombinant organism is derived from the fact that the desired product is produced as a fusion protein of the desired gene product and a fusion partner having, in relation to the final product, an undesired enzymatic side activity." Specification, page 1, lines 25-30. Thus, there is no need to actually make every possible starting material in order to practice the invention as the specification teaches that the simple steps of the invention may be

applied to chymosin compositions having undesired enzymatic activity.

The state of the prior art is ignored by the examiner as recombinant chymosin production has been achieved well in advance of the filing of the patent application. For instance, Ward et al., relied on by the examiner to reject the claims for obviousness is not even mentioned in the analysis of the state of the prior art provided by the examiner. Ward teaches improving production of chymosin in Aspergillus by expression as a glycoamylase-chymosin fusion protein.

The pending claims state bovine or *Camelidae* species. However, the claims as a whole are not directed merely to "an organism that is selected from the group consisting of a bacterial species, a yeast species and a species of filamentous fungi, wherein the organism comprises a gene for encoding chymosin that is derived from a bovine or *Camelidae* species," but include the process steps for solving a problem that the specification teaches arises from the use of such organisms. Specifically, the specification teaches "[i]n certain instances, an undesired enzymatic activity in a cultivation medium for a recombinant organism is derived from the fact that the desired product is produced as a fusion protein of the desired gene product and a fusion partner having, in relation to the final product, an undesired enzymatic side activity." Specification, page 1, lines 25-30. Furthermore, the specification provides an example of reducing glucoamylase activity derived from the cultivation of an organism expressing a prochymosin-glucoamylase fusion protein at page 9. Based on the foregoing, there is no question that the pending claims are enabled.

Under these circumstances it is improper for the examiner to require additional disclosure related to the specific organisms which might be used with the method of the pending claims. The claims are not directed to recombinant organisms themselves and as such do not require the same level of disclosure that would be required had the claims been directed to broad claims to

the organisms themselves. However, the examiner has analyzed the claims as though they were simply directed to the organisms themselves. Indeed, not once are the specific method steps of the claimed invention mentioned anywhere in the examiners enablement analysis. Appellant respectfully submits that when the claimed invention is considered as a whole there is no doubt that the specification conveys to the person of ordinary skill in the art that the applicant was in possession of the invention. Appellant further submits that the additional disclosure which the examiner would find necessary to comply with the enablement requirement is not required under 35 U.S.C. § 112, first paragraph. Accordingly, Appellant respectfully requests that the honorable Board reverse the rejection of claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for failure to comply with the enablement requirement.

C. Claims 5-6, 9, 12-14, 16-18, and 42-43 Are Non-Obvious Over Lawlis in view of Ward.

Before a *prima facie* case of obviousness can be established under 35 U.S.C. § 103, the *Graham v. John Deere* factors must be addressed. M.P.E.P. § 2141(I) states:

> Patent examiners carry the responsibility of making sure that the standard of patentability enunciated by the Supreme Court and by the Congress is applied in each and every case. The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated: Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquires may have relevancy. . .

"When evidence of secondary considerations such as unexpected results is initially before the Office, for example in the specification, that evidence should be considered in deciding whether there is a prima facie case of obviousness." M.P.E.P. § 2144.08.

If a reference does not explicitly teach a claim limitation, the claim limitation may

nevertheless be met inherently. However, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." M.P.E.P. § 2112 (quoting *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)). "The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *Id.* (citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), which reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art). Finally, Appellant submits that where the reason or motivation to modify a reference results from an inherent teaching in a prior art reference, the examiner must establish that a person of ordinary skill in the art would have recognized that the property is inherent in the reference at the time of the invention and without the benefit of having read the specification of the application being examined.

Lawlis teaches a cell killing technique that involves adding an organic acid in a medium and lowering the pH of the medium to 2 pH units below the pKa of the organic acid. Lawlis teaches that a "preferred acid is acetic acid because it is effective with a wide range of cells and because it is one of the lowest cost acids available." Lawlis, col. 4, lines 49-51. Acetic acid has a pKa of approximately 4.7, and thus Lawlis teaches lowering the pH to 2.79 in the cell killing step. Lawlis teaches expressing chymosin with *A. niger var. awamori* but does not teach glucoamylase activity or expression of a glucoamylase-prochymosin fusion protein. Lawlis differs from the claimed invention by failing to teach (1) a medium that "comprises a gene for encoding chymosin that is derived from a bovine or *Camelidae* species," and (2) "inactivat[ing]

at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity."

Recognizing that the preferred embodiment of Lawlis does not teach or suggest "a pH in the range of 1.0 to 1.8," the examiner turns to the general teaching of Lawlis that "[t]he process of this invention can be employed using any desired organic acid . . . ." Lawlis, col. 3, lines 51-52. As examples of "any desired organic acid," Lawlis also teaches that propionic acid (pKa=4.87) can be used and formic acid (pKa=3.75) can be used. Lawlis, col. 3, lines 51-64. The examiner focuses on Lawlis' teaching that formic acid can be used, ostensibly because in doing so one would lower the pH to 1.75. The examiner turns to the specification of this application and states that the claimed result of "inactivat[ing] at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity" would have been inherent in Lawlis. Appellant respectfully points out that in order to achieve the claimed result a person of ordinary skill in the art would have to (1) modify Lawlis such that it produces a medium in which glucoamylase activity is present, and (2) select a non-preferred organic acid such a lactic acid that happens to have a pKa below 4.0. The missing claim element does not in fact "necessarily flow" from the teachings of Lawlis. Instead, various modifications to the teaching of Lawlis must be made in order to achieve the claimed effects of the invention. Thus, Lawlis does not inherently teach "inactivat[ing] at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity."

The examiner acknowledges that Lawlis does not teach a medium comprising both chymosin and glucoamylase activity, and cites Ward to cure this deficiency. *See* Final Office Action, page 11. Ward is discussed at page 2, lines 19-23, of the specification. Ward differs from the claimed invention in that there is no step of: "subjecting said medium to a pH in the

range of 1.0 to 1.8 for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity." Ward teaches improved production of bovine chymosin in recombinant *Aspergillus* by expression of a glucoamylase-chymosin fusion protein. *See* Ward, Title & Abstract. In particular, Ward teaches that the glucoamylase-chymosin fusion proteins can be secreted at higher efficiency compared to prochymosin. Ward, page 438, col. 1, last paragraph. Ward teaches that lowering the pH to 2 converts the fusion protein to chymosin and at least some pseudochymosin. Ward, page 439, col. 2, first paragraph. Ward teaches that "[p]resumably, this would eventually be further processed to mature chymosin under appropriate conditions." Ward, page 439, col. 2, first paragraph. Ward further teaches that "[p]seudochymosin is fairly stable at a pH below 3 or above 6 but is further processed to mature chymosin at pH 4.5." Ward, page 435, col. 1, first paragraph after the Abstract. Thus, Ward suggests raising the pH to 4.5 after activating the chymosin at a pH of 2.0 to convert any pseudochymosin to chymosin.

In the paragraph bridging pages 11-12 of the Final Office Action, the examiner states that the invention is rendered obvious by combining the formic acid cell kill of Lawlis with the composition taught by Ward. Appellant would respectfully point out that it is only through hindsight that a person of ordinary skill in the art would select a non-preferred organic acid listed within the disclosure of Lawlis and combine it with Ward. Lawlis specifically teaches at col. 4, ll. 49-54:

> A preferred acid is acetic acid because it is effective with a wide range of cells and because it is one of the lowest cost acids available. Other effective acids can be used depending on the cell cultures involved and the economics of the process.

It should also be noted that none of the cited references teach that substantial chymosin activity

can be maintained below a pH of 2.0, which is only taught by applicant's own disclosure.

Finally, "[w]hen evidence of secondary considerations such as unexpected results is initially before the Office, for example in the specification, that evidence should be considered in deciding whether there is a prima facie case of obviousness." M.P.E.P. § 2144.08. As discussed above, the claims require "subjecting said medium to a pH in the range of 1.0 to 1.8 for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity." Prior to the present invention, the removal of unwanted side activity in chymosin preparations often involved complicated phase-separation and chromatographic processes. See Specification, page 3. None of the references discussed or cited by the examiner discuss reduction of glucoamylase activity utilizing changes in pH. Moreover, none of the cited references teach that this can be accomplished without destroying the chymosin activity. The examiner improperly side-steps consideration of unexpected results by stating that they are "an inherent result of practicing the method suggested by the prior art." Final Office Action, page 13. However, it is improper to disregard unexpected results in this manner, especially where as here there is no showing that the unexpected results would have been recognized or appreciated by a person having ordinary skill in the art at the time of the invention. For the foregoing reasons, Appellant respectfully requests that the honorable Board reverse the rejection of claims 5-6, 9, 12-14, 16-18, and 42-43 as being unpatentable over Lawlis in view of Ward.

VIII. CONCLUSION

In view of the foregoing, Appellant respectfully requests that the Board reverse the rejections set forth in the Final Office Action.

Respectfully submitted,

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Dated: November 2, 2007 By: _____

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IX. CLAIMS APPENDIX

Appealed Claims:

Claim 5. A method according to claim 9, wherein at least 90% of said glucoamylase activity is inactivated.

Claim 6. A method according to claim 9, wherein the medium having a pH of 2.0 or higher is a medium derived from the cultivation of an organism that during its cultivation produces said chymosin activity and said glucoamylase activity.

Claim 9. A method for reducing the glucoamylase activity in a milk clotting composition comprising the steps of:

(i) providing a medium having a pH of 2.0 or higher that comprises chymosin activity and glucoamylase activity, wherein the medium having a pH of 2.0 or higher is derived from the cultivation of an organism that is selected from the group consisting of a bacterial species, a yeast species and a species of filamentous fungi, wherein the organism comprises a gene for encoding chymosin that is derived from a bovine or *Camelidae* species, and

(ii) subjecting said medium to a pH in the range of 1.0 to 1.8 for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity.

Claim 10. A method according to claim 9, wherein the bacterial species is selected from the group consisting of a gram negative bacterial species and a gram positive species.

Claim 11. A method according to claim 9, where the yeast species is selected from the group consisting of *Saccharomyces cerevisiae*, a methylotrophic yeast species and a *Klyuveromyces* species.

Claim 12. A method according to claim 9, wherein the species of filamentous fungi is selected from the group consisting of an *Aspergillus* species, a *Cryphonectria* species, a *Fusarium* species, a *Rhizomucor* species and a *Trichoderma* species.

Claim 13. A method according to claim 9, wherein the medium having a pH of 2.0 or higher is subjected to a pH in the range of 1.5 to 1.8.

Claim 14. A method according to claim 9, wherein the medium having a pH of 2.0 or higher is subjected to a pH between 1.7 to 1.8.

Claim 16. A method according to claim 9, wherein the medium having a pH of 2.0 or higher is subjected to a pH of approximately 1.8.

Claim 17. A method according to claim 9, wherein the pH in the range of 1.0 to 1.99 is provided by adding an inorganic or an organic acid.

Claim 18. A method according to claim 9, wherein said period of time is in the range of 0.1 minutes to 48 hours.

Claim 35. A method according to claim 10, wherein the bacterial species is selected from *E. coli* and *Bacillus*.

Claim 36. A method according to claim 9, wherein the yeast species is selected from *Pichia pastoris* and *Klyuveromyces lactis*.

Claim 39. A method according to claim 9, wherein the *Camelidae* species is *Camelus dromedarius*.

Claim 42. The method of claim 12, wherein said *Aspergillus* species is *Aspergillus niger* var. *awamori*.

Claim 43. The method of claim 9, wherein at least 85% of the chymosin activity is maintained in step (ii).

X. EVIDENCE APPENDIX

None

XI. RELATED PROCEEDINGS APPENDIX

None